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PRACTICE

RATIONAL TESTING

Investigating cortisol excess or deficiency: a practical approach

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What you need to know

- Random, untimed cortisol levels are of limited clinical value
- Cortisol measured at around 8-9 am (when the level is expected to be highest) is the preferred initial screening test for cortisol deficiency
- If high clinical suspicion for hypercortisolaemia, patients should be referred to specialist care for testing and interpretation of results
- Dynamic testing is often required to confirm cortisol deficiency or excess given the pulsatile nature of cortisol secretion and the influence of diurnal variation, feedback control and stress.
- Salivary cortisol has better specificity for diagnosis of Cushing's syndrome than urinary cortisol and is easier to collect; if this test is available, it is increasingly preferred to urinary free cortisol

A 67 year old woman with no significant medical history required urgent orthopaedic surgery after a fall. In preparation, her bloods were collected and a random cortisol was requested, which came back at 763 nmol/L. She did not have diabetes or hypertension. The anaesthetist reviewed and commented: "High cortisol, not safe for surgery until further evaluation."

A 24 year old man with previously well controlled type 1 diabetes presented with repeated hypoglycaemic episodes. Serum cortisol in clinic at 9 am came back as 143 nmol/L.

Cortisol, secreted by the adrenal cortex, regulates blood pressure, glucose metabolism, and physiological responses to stress. Both cortisol over-secretion (hypercortisolism, Cushing's syndrome) and under-secretion (hypocortisolism such as in Addison's disease) are uncommon: the prevalence of Addison's disease is 6-9 per 100 000,[1] while that of Cushing's syndrome is 4/100 000.[2] However, given the potential for life threatening consequences (such as in acute adrenal crisis) and the range of associated non-specific symptoms, it is critical for clinicians to understand how to interpret and manage cortisol status. Cortisol excess could be due to an adrenal cortisol-secreting tumour or to a functional pituitary tumour (Cushing's disease), or, less commonly, malignant tumours can secrete adrenocorticotrophic hormone (ACTH) ectopically. Cortisol deficiency could be due to primary adrenal malfunction (such as autoimmune-mediated atrophy "Addison's disease," malignant infiltration, or haemorrhage) or secondary to either pituitary or hypothalamic disease resulting in reduced secretion of ACTH.

Interpreting cortisol results can be confusing because cortisol secretion is pulsatile, shows diurnal variation, is regulated via a feedback system, and is influenced by a range of stressors. Furthermore, the tests involve measuring cortisol on its own (static testing) or as part of a stimulation or suppression test (dynamic function testing), and in a range of sample types (such as from serum, saliva, or urine).

This article is aimed at non-specialist doctors who may need to order or interpret cortisol blood tests. Grounded in cortisol physiology, it describes how you might investigate suspected cortisol deficiency and excess, the practicalities of sample choice, and correct timing to obtain meaningful results.

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, Division Chief, Clinical Chemistry, Sidra Medical and Research Center, Qatar; honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages: https://www.bmj.com/about-bmj/resources-authors/article-types.

Sources and selection criteria

This article is based on targeted search of online publication databases (https://www.nlm.nih.gov/) examining the topic areas listed in the article, including:

- Cortisol physiology, including factors affecting cortisol production
- Cortisol measurement
- Biochemical identification of cortisol excess and deficiency
- Clinical presentation of cortisol excess and deficiency.

Secondary references were identified originating for those identified above, in addition to those identified through personal and professional networks (including grey literature, such as professional guidelines), and throughout the review process.

Factors affecting cortisol production and measurement

Cortisol is secreted from the adrenal cortex and is influenced by (fig 1):

Circadian rhythm—Cortisol is secreted in response to pulses of corticotrophin releasing hormone (CRH) and ACTH.[3] These pulses contribute to a circadian rhythm with peak cortisol levels just before waking and the nadir around bedtime. Hence, if cortisol deficiency is suspected, cortisol should be measured at around 8-9 am (when it is expected to be highest). If this is low, it would suggest deficiency. If excess cortisol is suspected, cortisol levels should be checked when they are expected to be lowest (around midnight). A random, untimed cortisol measurement is of minimal clinical value and should be avoided in assessing cortisol status.

Feedback control—Exploiting the physiologic feedback mechanisms is the underlying principle behind dynamic function tests (both stimulation and suppression tests).[4 5] CRH produced in the hypothalamus stimulates the pituitary to produce ACTH, which stimulates the adrenal gland to produce and release cortisol.[3 6] Rising cortisol levels suppress further CRH and ACTH production, thereby creating a negative feedback loop. In cases of cortisol insufficiency due to adrenal causes, CRH and ACTH levels are expected to be high. However, in cases of cortisol insufficiency due to a hypothalamic or pituitary cause (such as a tumour), the ACTH level would be low. The same principles apply to cortisol excess.

Stress—Cortisol is often referred to as the stress hormone. Its secretion is promptly induced in response to a range of stressors including severe trauma, sepsis, pain, anxiety, exercise, and hypoglycaemia. The extent of impact on cortisol levels will depend on the severity of the stress. If there is suspicion of cortisol deficiency (for example, unexplained hyponatraemia, hypoglycaemia, or hypotension in a severely septic patient), interpretation of cortisol levels should take into account the underlying stress.[7]

Cortisol binding globulin—Cortisol is bound strongly to cortisol binding globulin (CBG) in serum. Serum cortisol measurement reflects the total rather than free concentration. Factors affecting CBG, such as acute illness or medicines such as hormonal contraception, could alter reported serum cortisol without having a bearing on free cortisol concentrations. In contrast, saliva and urine samples reflect the free component of cortisol and may thus be clinically more useful. For example, in a recent study, women taking the contraceptive pill were found to have total plasma cortisol and CBG levels 2.9 and 2.6 times higher, respectively, when compared with controls, whereas 24 hour urinary free cortisol and plasma free cortisol were not significantly different.[8] Given the wide availability of total serum cortisol assays (which includes the CBG-bound component), the effect of CBG may need to be taken into consideration.

Exogenous glucocorticoids used for the treatment of other diseases may also suppress the hypothalamo-pituitary-adrenal axis. This includes the use of inhaled, nasal, transdermal, and intra-articular preparations.

When to consider measuring cortisol in routine clinical practice?

Given the multi-organ impact of cortisol, its measurement may be considered in a wide range of clinical scenarios in day-to-day practice. However, adrenal disorders are uncommon. Cortisol measurement is not routinely required unless there are specific features to suspect adrenal disease. For example, rapid onset of diabetes with weight gain, easy bruising, and muscle weakness could point to possible Cushing's syndrome. Paradoxically, unexplained hypoglycaemia or hypotension developing in a patient with type 1 diabetes or thyroid disease should raise suspicion for Addison's disease. Box 1 lists some of the clinical features that should prompt a clinician to consider measuring cortisol.

Box 1: When to consider testing cortisol function

Cortisol deficiency[9 10]

- Unexplained electrolyte imbalance (hyponatraemia, hyperkalaemia)
- Hypotension (especially if resistant or associated with other factors such as weight loss, electrolyte imbalance, increased pigmentation)
- Unexplained or accelerated weight loss
- Tiredness (unexplained, overwhelming, or associated with other above symptoms)
- Unexplained reduced appetite, salt cravings, increased thirst or urination, nausea and vomiting
- Combinations of autoimmune disease (such as type 1 diabetes, hypothyroidism or hyperthyroidism, vitiligo, pernicious anaemia, chronic active hepatitis, alopecia, coeliac disease, rheumatoid arthritis)
- Family history of autoimmune disease (as above)
- Hypothyroidism with expected or confirmed autoimmune disease
- Type 1 diabetes with recurrent unexplained hypoglycaemia
- Cancer with bilateral adrenal lesions
- Use of exogenous corticosteroids
- Pregnancy with unexplained persistent nausea, hypotension, and/or fatigue[11]

Cortisol excess[11]

- Unexplained electrolyte imbalance (hypokalaemia)
- Hypertension (especially in young patients, resistant to treatment, or associated with diabetes, central obesity, increased bruising)
- Unexplained or accelerated weight gain
- Deteriorating diabetes control
- Unexplained bruising
- Adrenal incidentaloma

Cortisol excess could be due to a cortisol-secreting tumour or to a functional pituitary tumour (Cushing's disease) secreting ACTH that is not responsive to the normal negative feedback loop. Less often, malignant tumours can secrete ACTH ectopically. Cortisol deficiency could be due to primary adrenal malfunction (such as autoimmune-mediated atrophy "Addison's disease," malignant infiltration, or haemorrhage) or secondary to either pituitary or hypothalamic disease resulting in reduced secretion of ACTH.

What tests are available and how to interpret them

In general, initial testing consists of static tests that are timed to correspond with physiologic diurnal cortisol variation:

- If cortisol excess is suspected, midnight cortisol should be measured
- If cortisol deficiency is suspected, cortisol levels should be checked at 8-9 am.

Cortisol testing modalities for both excess and deficiency (with their advantages and disadvantages) are summarised in table 1.

If initial static tests are abnormal, dynamic tests are then used to confirm abnormal results. The approach to testing is depicted in figure 2.

Investigating suspected cortisol excess

There are three tests that can be considered initial screening tests when investigating suspected hypercortisolism. These are midnight serum or salivary cortisol, 24 hour urinary free cortisol, and the overnight dexamethasone suppression test. Serum testing was extensively used in the past, but it requires hospitalisation and venepuncture at midnight, causing stress that could falsify the results. If available, salivary cortisol is increasingly being used for outpatient testing instead (mostly by specialists). Although an overnight dexamethasone suppression test is a dynamic test, it can be performed as an outpatient, and GPs could consider this test with select patients, particularly when clinical suspicion is low and testing can be done quickly to rule out cortisol excess.

While many of these tests can, in theory, be performed by general practitioners, if they have a high clinical suspicion of hypercortisolism, we recommend referral to specialist care for testing because of the complexity of interpreting the results and potential confounders. See table 1 for a summary of the non-dynamic tests that could be used to test for cortisol excess.

Baseline (non-dynamic) tests

Serum cortisol—A random cortisol measurement is of limited clinical value when testing for cortisol excess.

Urinary cortisol—Urinary cortisol testing relies on urine collection over 24 hours to measure the cumulative cortisol produced in that time. Although the diagnostic sensitivity and specificity vary between studies, an elevated 24 hour urinary cortisol level has been found to be 84-93% sensitive and 56-79% specific for diagnosis of Cushing's syndrome.[12 13]

Salivary cortisol—Salivary cortisol has better specificity than urinary cortisol and is useful for ruling out cortisol excess. A value above the reference interval has an average sensitivity of 95% and specificity of 91.6%, depending on the assay used and the locally derived cut-off value,[14] for the diagnosis of Cushing's syndrome. Because it is easier to collect and has the advantage of measuring free rather than bound cortisol, salivary cortisol has been advocated as a first line test.[13] However, salivary cortisol assays have limited availability. On balance, clinicians have to rely on the tests that are available locally: if urinary cortisol is the only available test, then it will be the first choice, to be followed by other investigations or referrals as required.

Dynamic testing: the dexamethasone suppression test

There are different methods for performing this test.[15] The overnight 1 mg dexamethasone suppression test can be performed on an outpatient basis and consists of a patient taking 1 mg of dexamethasone orally between 11 and 12 pm and then a serum cortisol sample being taken at 9 am the following morning.[16] A cortisol level of <50 nmol/L has high sensitivity (95%) and moderate specificity (80%) for excluding Cushing's syndrome. It is important to note that some drugs can interfere with the test results by accelerating dexamethasone metabolism (such as antiepileptics and rifampicin) or impairing it (such as diltiazem and fluoxetine). Other drugs, such as oestrogens and carbamazepine, increase the concentration of cortisol binding globulin, resulting in falsely elevated cortisol levels. Other forms of the dexamethasone suppression test (such as the two day, low dose test) are available and could be considered by endocrinologists.

Further testing

Once cortisol excess is confirmed, the source of excess production along the hypothalamo-pituitary-adrenal axis (or ectopic ACTH secretion) needs to be identified, typically by an endocrinologist.

Investigating suspected cortisol deficiency

For initial screening of suspected cortisol deficiency, an 8-9 am cortisol sample is taken to measure cortisol at its expected peak. Unless the results are reassuring, further discussion or referral to endocrinology is required. See figure 2 for details.

Non-dynamic serum cortisol testing

Deficiency is highly unlikely if the 8-9 am cortisol level is above 400-475 nmol/L (the exact cut-off will vary depending on the assay used in the local laboratory). Recent work proposed that values between 336 and 506 nmol/L had a 100% specificity of predicting passing a short synacthen test.[17] Cortisol levels <150 nmol/L at 8-9 am warrant immediate discussion with, or referral to, endocrinology, and hydrocortisone replacement should be started urgently. Cortisol levels between 150 and 400 nmol/L (or agreed limit from the local laboratory) require further evaluation to rule out cortisol deficiency. If the sample was not collected at 8-9 am, then a repeat cortisol measurement can be performed. If the sample was collected correctly, patients with levels below 400-475 nmol/L (depending on the local assay limit), will need follow-up testing with a specialist.

Neither urinary nor salivary cortisol has a role in the assessment of cortisol deficiency.[18]

Dynamic tests: short synacthen test

Synacthen mimics the effect of ACTH in stimulating cortisol production: administration of synacthen should therefore result in a predictable rise in serum cortisol.[5] The short synacthen test has equivalent performance to that of the gold standard insulin stress test.[4 19 20] As it can be performed in an outpatient setting, it has become the most common dynamic test of cortisol deficiency. The cut-off values for a satisfactory response depend on the cortisol assay used[9]: 450 nmol/L is the threshold used in many centres, though this again will need to align with the local assay.[21]

Falsely reassuring test results could be obtained in a case of (*a*) early pituitary failure before adrenal atrophy develops or (*b*) postoperative testing in patients who had recently undergone

surgical removal of the pituitary gland for Cushing's syndrome (as persistent adrenal hypertrophy may lead to adequate response).

The role of ACTH measurement

ACTH is almost always measured by specialists to determine the source of cortisol excess or deficiency along the hypothalamic-pituitary-adrenal axis. For example, in a case of cortisol excess, low ACTH levels point to an adrenal source. In practice, for the assessment of cortisol deficiency, baseline ACTH is measured only if the short synacthen test result is abnormal.

Exogenous steroids and impact on cortisol measurement: a pragmatic approach

Patients taking oral glucocorticoids at a dose higher than the physiological cortisol level (prednisolone 5 mg or dexamethasone 1-2 mg daily) will have a suppressed pituitary-adrenal axis. They may need tapered withdrawal of their glucocorticoids (box 2), but do not need to have their cortisol concentrations measured routinely.

Box 2: Tapering exogenous glucocorticoids: impact on cortisol measurement

- Most steroid courses are short (<3 weeks), and so adrenal atrophy is unlikely and cortisol measurement is not routinely required
- For longer steroid courses (>3 weeks) at higher than physiological doses, gradual reduction is necessary; again cortisol testing is not required. If patients feel unwell during steroid withdrawal, they need to seek medical advice to consider more gradual withdrawal
- In cases of prolonged steroid courses (such as for polymyalgia rheumatic, which may require courses of several months), more gradual withdrawal and careful monitoring of symptoms is warranted and is sufficient in most cases. Cortisol measurement, if required, should be part of specialist evaluation

Case resolution

In the first case, given the absence of clinical features of Cushing's syndrome in this 67 year old woman with physiological stress due to injury, an elevated random cortisol level requires no further action and should not delay orthopaedic management. However, for further reassurance, we would recommend that the woman is reassessed when she is well.

In the second case, the 9 am cortisol test result <150 nmol/L required immediate further investigation to rule out cortisol insufficiency. A dynamic, confirmatory test was performed along with ACTH testing. Serum cortisol was low and ACTH was elevated, confirming the diagnosis of primary adrenal insufficiency. Starting hydrocortisone resulted in resolution of the hypoglycaemic episodes.

Education into practice

- How do you ensure accurate timing for collection of a 9 am serum cortisol sample?
- Audit the cortisol requests made in the past six months in your practice and review the timings and results in relation to the recommendations in this article.
- Reflect on the last time you considered an adrenal disorder in your practice. Would the recommendations in this article alter your management plan?

How patients were involved in the creation of this article

No patient involvement. The cases provided are fictitious but based on commonly encountered clinical scenarios.

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Table

Table 1| Advantages and disadvantages of different options for cortisol sampling

Procedure	Requirements	Advantages	Disadvantages
Serum sample			
• Random, untimed cortisol is of limited clinical value	• Early morning (8-9 am) sample for assessing cortisol deficiency • Late evening (11-12 pm) sample for assessing cortisol excess	• Test widely available • Well characterised cut-off concentrations	• Invasive test (venepuncture)–Could lead to stress induced hypercortisolaemia, especially if sample collected at midnight • Measures total, not free cortisol, so vulnerable to abnormalities in cortisol binding globulin (CBG): - During critical illness, CBG may fall and the consequent low total cortisol may be mistaken for adrenal insufficiency - Oral contraceptives (oestrogen component) or pregnancy result in increased CBG, spuriously raising total cortisol levels (but not influencing free cortisol) • Interference from exogenous steroids in some assays • Interference from cortisol precursors in some assays
Saliva sample			
• Better specificity for diagnosis of Cushing's syndrome than urinary cortisol and easier to collect	• Use synthetic swab or passive drool (0.5 mL)	• Non-invasive test • Home collection possible • Convenient for midnight samples • Measures free cortisol • Overcomes stress induced hypercortisolaemia • Stability at 4°C for 2 weeks • Food and blood contamination have no impact if sampling instructions are followed	• Patients taking diuretics may find it difficult to collect enough saliva (dry mouth) • Food or blood contamination (collect ≥60 min after eating or cleaning teeth) • Restricted availability—May need to send samples to specialist laboratories, with implications for cost and turnaround times • Only of use in identifying cortisol excess • Potential for "user error" in self sampling of saliva
Urine sample			
	• 24 hour collection	• Non-invasive test • Outpatient test • Measures free cortisol • Measurement widely available	• Samples may not represent a full 24 hour collection • Metabolites may interfere with some assays • Only of use in identifying cortisol excess • Lower sensitivity and specificity for ruling out hypercortisolaemia than other methods

Figures

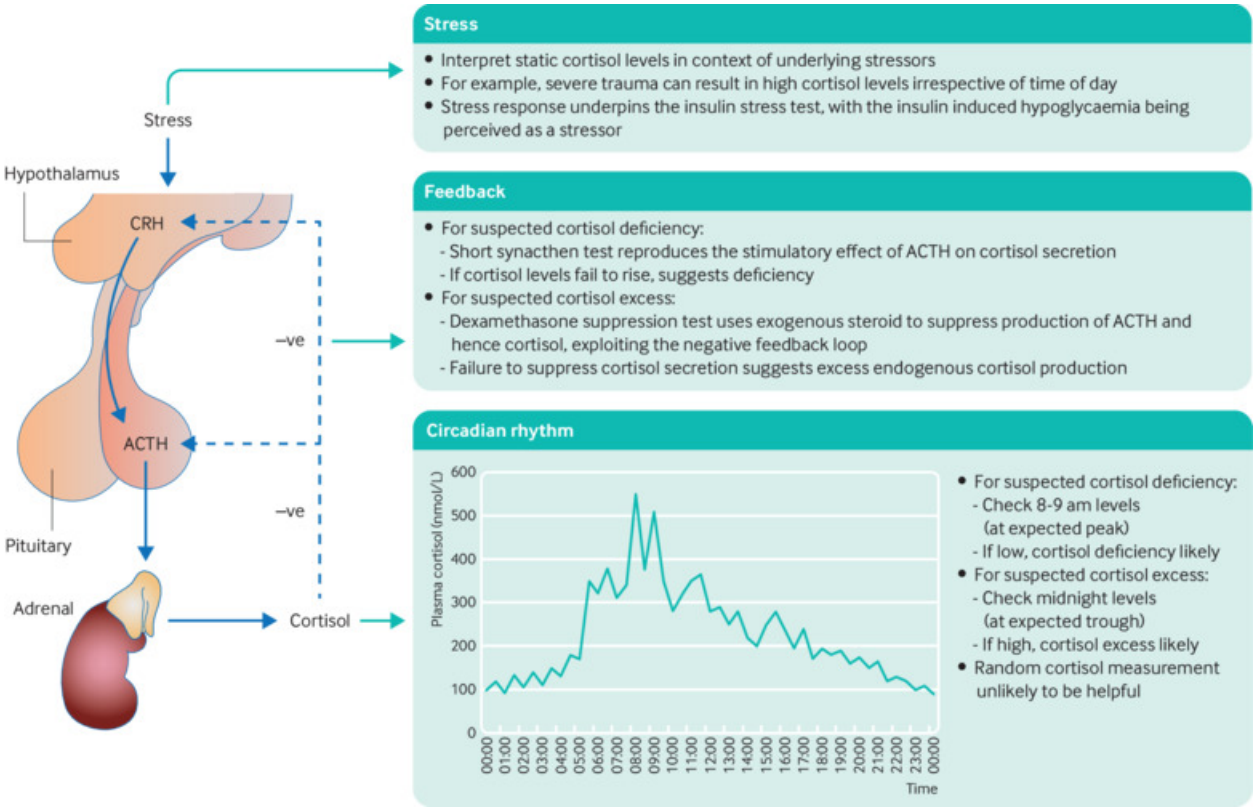

Fig 1 How cortisol testing is affected by its underlying physiology

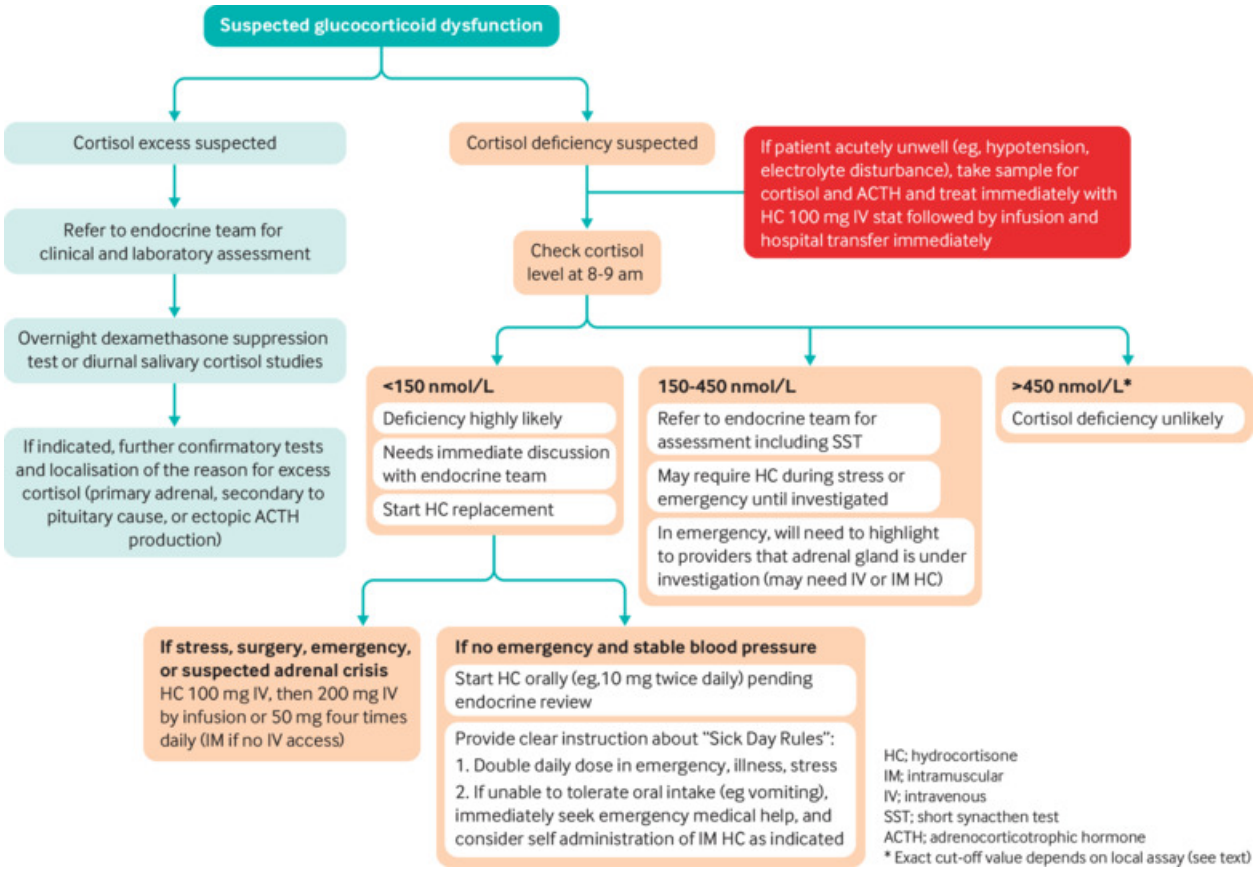

Fig 2 Action plan for suspected glucocorticoid dysfunction